REMARKS

This Amendment deletes language added by the previous amendment to claim 23. Claims 23 and 25-33 are pending.

This Amendment overcomes the objection to claim 23 by deleting the typographical error noted by the Patent Office. Reconsideration and withdrawal of the objection to claim 23 are respectfully requested.

This Amendment overcomes the 35 U.S.C. § 112, first paragraph, rejection of claims 23 and 25-33. The phrase "all or substantially all of the active ingredient" has been deleted from claim 23. Reconsideration and withdrawal of the "new matter" rejection of claims 23 and 25-33 are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 23, 25-29 and 31-33 over Huupponen et al., 58 Clin.Pharmacol.Ther. 506-11 (1995) in view of U.S. Patent No. 5,498,623 to Karjalainen et al. is traversed. The claimed method of administration requires a formulation containing fipamezole [4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt] to be administered to a patient by oromucosal administration, in which the active ingredient is absorbed via oral mucosa.

The applicants have discovered the problem of QTc prolongation[1] (encountered when fipamezole is orally administered) is avoided when fipamezole is oromucosally administered. See Example 8 of the application and the Declaration Pursuant to 37 C.F.R. § 1.132 filed February 17, 2009.

Summary of Argument

- Karjalainen et al. discloses the compound, fipamezole, and that this novel compound possesses certain advantageous pharmacological properties. Karjalainen et al. teaches the compound may be administered orally, parenterally or intravenously, with oral administration preferred.

- Oral administration of fipamezole causes QTc prolongation, a dangerous side effect. This side effect is dose-dependent, increasing in severity with increasing circulating concentrations.

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[1]QTc interval is the time required for cardiac ventricular depolarization and subsequent repolarization. Prolongation of the QTc interval can increase a patient's risk of arrhythmia. The FDA has published guidance for nonclinical evaluation of QT interval prolongation by human pharmaceuticals, and several drugs have been removed from the market because they directly or indirectly prolong the QTc interval. In short, QTc prolongation is a significant issue confronting those skilled in the art of drug synthesis and development.

- Huupponen et al. teaches that oromucosal administration of atipamezole significantly increases atipamezole's bioavailability as compared to oral administration: oromucosal administration leads to circulating levels of atipamezole more than an order of magnitude greater than that achieved by oral administration of an equal dose.

- Based on the teachings of Huupponen et al., the ordinarily skilled artisan would have expected that oromucosal administration of fipamezole would analogously increase its bioavailability, increasing circulating levels of fipamezole as compared to levels achieved by oral administration of an equal fipamezole dose. As a consequence, the person of ordinary skill would have expected oromucosal administration of fipamezole to ***increase*** fipamezole's dose-dependent side effect.

- The present inventors discovered, however, that while oromucosal administration of fipamezole does indeed increase its bioavailability, and thus its circulating concentrations, ***as expected*** based on the teachings of Huupponen et al., oromucosal administration ***unexpectedly*** eliminates the side effect of QTc

prolongation. This result could not have been predicted from Karjalainen et al., which is silent with respect to fipamezole's side effects, and silent regarding oromucosal administration, nor could this result have been predicted from Huupponen et al., since atipamezole, unlike fipamezole, does not cause QTc prolongation. Neither would this result have been predicted from any other information in the prior art - indeed, to this day, the pharmacokinetic and/or physiological basis for the elimination of QTc prolongation side effects by oromucosal administration of fipamezole is unknown.

Detailed Discussion

The absence of QTc prolongation when fipamezole is oromucosally administered is an unexpected result which rebuts any *prima facie* case of obviousness raised by the combination of Huupponen et al. and Karjalainen et al. In this regard, evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). When a patent applicant puts forth rebuttal evidence, the Board must consider that

evidence. In re Sullivan, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007), see also In re Soni, 54 F.3d 746, 750, 34 USPQ2d 1684 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability"). The absence of a property which would be expected by those of ordinary skill in the art can overcome a *prima facie* case of obviousness. See, for example, Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 89 USPQ2d 1370 (Fed. Cir. 2008) (holding isolated stereoisomer non-obvious over racemic mixture in view of absolute stereoselectivity of claimed dextrorotary enantiomer which provides all of the desired antiplatelet activity and none of the adverse neurotoxicity), and In re May, 574 F.2d, 1082, 1090-94, 197 USPQ 601 (CCPA 1978)(holding isolated levo stereoisomer nonobvious over racemic mixture of stereoisomers, after conceded *prima facie* showing of obviousness, because isolated stereoisomer was unexpectedly non-addictive).

1. The Applicants Compared the Claimed Method of Administration to the Closest Prior Art

Karjalainen et al. discloses fipamezole, its preparation and use as an antagonist to α_2-adrenoceptors. The compound may be administered orally, parenterally or intravenously, with oral administration preferred (Col. 4, lines 60-64). The *only*

difference between the claimed method and Karjalainen et al. is the mode of administration. Accordingly, the question of whether the claimed method produces an unexpected result is properly considered against Karjalainen et al. rather than Huupponen et al., which is directed to a different compound. Boesch, supra.

2. The Absence of QTc Prolongation Resulting From Oromucosally Administered Fipamezole is Unexpected

The cited references fail to disclose or suggest that oromucosal administration of fipamezole will avoid QTc prolongation. Huupponen et al. teaches oromucosal administration of atipamezole - a non-fluorinated imidazole - results in increased bioavailability and more uniform absorption than oral administration of atipamezole. Karjalainen et al. teaches its imidazole compounds (including fipamezole and antipamezole) may be administered orally, parenterally or intravenously. Neither reference contains any disclosure regarding the problem of QTc prolongation. However, further investigation of fipamezole revealed its tendency to prolong QTc interval when orally administered.

A. QTc Mechanism Unrelated to Administration - One of ordinary skill in the art would not normally expect a change of administration route to significantly affect QTc prolongation.

Instead, those of ordinary skill in the art believe the mechanism of QTc prolongation is linked to modification of the action potential, which is based on the balance between the inflow of positive ions (sodium and calcium) and the outflow of positive ions (potassium). See Crouch et al., "Clinical Relevance and Management of Drug-Related QT Interval Prolongation," 23 Pharmacotherapy 881 (2003) beginning at 882, right col., line 3. In short, those of ordinary skill in the art believe QTc prolongation is an electrochemical phenomenon rather than caused by a particular route of administration.

B. An Expected Result of Oromucosal Fipamezole Administration is Enhanced Bioavailability

One of ordinary skill in the art who combined the disclosure of Huupponen et al. and Karjalainen et al. would reasonably expect oromucosal administration of fipamezole to result in enhanced bioavailability in comparison to oral administration of fipamezole. Importantly, QTc prolongation caused by oral administration of fipamezole increases with increasing concentration[2]. One of

[2]The declaration's data demonstrates QTc prolongation caused by oral administration of fipamezole increases with increasing dosage. A 5 mg/kg/day dosage prolonged the QTc interval by 14.0 ms and a 10 mg/kg/day dosage prolonged the QTc interval by 25.0 ms. See paragraph 4F, last subparagraph on page 7, and Fig. 1 of the declaration.

ordinary skill, aware of the dosage dependent QTc prolongation problem resulting from oral administration of fipamezole, would believe oromucosal administration would result in longer QTc prolongation due to the increased bioavailability to be expected from oromucosal administration of fipamezole, as suggested by Huupponen et al. Thus, the absence of QTc prolongation when fipamezole is oromucosally administered would be considered unexpected and surprising in view of the QTc prolongation resulting from oral administration of fipamezole, Sanofi-Synthelabo and May, supra.

C. QTc Prolongation is Unpredictable

Those skilled in the art recognize testing is required to determine whether a given compound will prolong QTc. See the FDA's Guidance for Industry S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (FDA October 2005).

The claimed method of administration produces an unexpected result (no QTc prolongation) which is unexpected, unpredictable and therapeutically significant, and thus weighs heavily in favor of non-obviousness of the claimed method. Reconsideration and withdrawal of the obviousness rejection of claims 23, 25-29 and 31-

33 over Huupponen et al. in view of Karjalainen et al. are earnestly requested.

The 35 U.S.C. § 103(a) rejection of claims 23 and 25-33 over Huupponen et al. and Karjalainen et al., further in view of U.S. Patent No. 6,413,988 to De Proost, is traversed for the reasons discussed above. De Proost is not directed to α_2-adrenergic receptor antagonists, and does not disclose any information concerning oromucosal vs. oral administration of fipamezole. Accordingly, the additional disclosure of De Proost does not detract from the unexpected and surprising result achieved by the claimed method of administration. Reconsideration and withdrawal of the obviousness rejection of claims 23 and 25-33 over Huupponen et al. and Karjalainen et al., further in view of De Proost, are earnestly requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 23 and 25-33, and issuance of a Notice of Allowance directed to these claims, are respectfully requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is requested to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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